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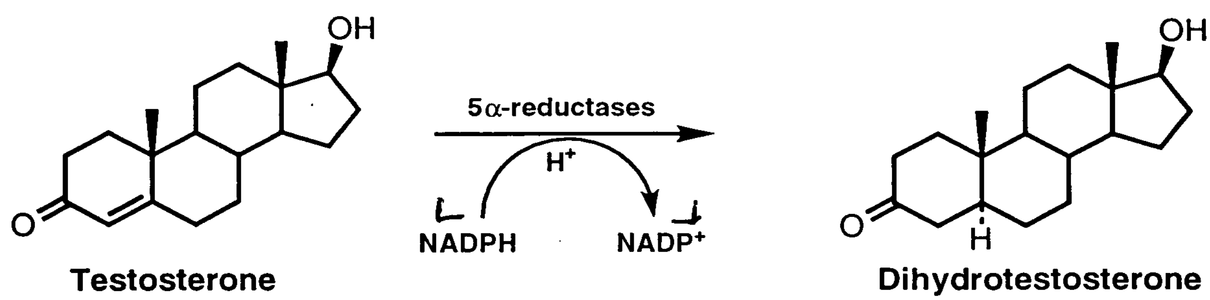
ANDROSTENONE DERIVATIVE

pending This patent application is a continuation-in-part of PCT application No. PCT/US94/10530, filed ~~16/09/94~~ September 16, 1994 in the name of Glaxo Inc.

The present invention relates to a particular 17β-anilide-4-aza-5α-androst-1-en-3-one derivative, as a surprisingly potent and selective dual inhibitor of type 1 and 2 human 5α-reductase.

BACKGROUND OF THE INVENTION

Androgens are responsible for many physiological functions in both males and females. Androgen action is mediated by specific intracellular hormone receptors expressed in androgen responsive cells. Testosterone, the major circulating androgen, is secreted by Leydig cells of the testes under the stimulation of pituitary-derived luteinizing hormone (LH). However, reduction of the 4, 5 double bond of testosterone to dihydrotestosterone (DHT) is required in some target tissues, such as prostate and skin, for androgen action. Steroid 5α-reductases in target tissues catalyze conversion of testosterone to DHT in an NADPH dependent fashion as shown in Scheme A.



SCHEME A

The requirement for DHT to act as an agonist in these target tissues has been highlighted by studies of steroid 5α-reductase deficient individuals who have vestigial prostate glands and do not suffer from acne vulgaris or male pattern baldness (see McGinley, J. *et al.*, *The New England J. of Medicine*, **300**, 1233 (1979)). Thus, inhibition of the conversion of testosterone to DHT in these target tissues is anticipated to be useful in the treatment of a variety of androgen responsive diseases, *e.g.*, benign prostatic hyperplasia, prostate cancer, acne, male pattern baldness and hirsutism.

Additionally, it has recently been discovered that two isozymes of 5α-reductase exist in humans which differ in their tissue distribution, affinity for testosterone, pH profile and sensitivity to inhibitors (see Russell, D.W. *et al.*, *J. Clin. Invest.*, **89**, 293 (1992); Russell, D.W. *et al.*, *Nature*, **354**, 159 (1991)). The steroid 5α-reductase deficient individuals studied by Imperato-McGinley are deficient in the type 2, 5α-reductase enzyme (Russell, D.W. *et al.*, *J. Clin. Invest.*, **90**, 799 (1992); Russell, D.W. *et al.*, *New England J. Med.*, **327**, 1216 (1992)), which is the predominant isozyme present in the prostate, while the type 1 isozyme is predominant in the skin. The relative value of isozyme specific and dual inhibitors of the two isozymes of 5α-reductase will depend upon the type of disease treated (benign prostatic hyperplasia, prostate cancer, acne, male pattern baldness or hirsutism) as well as the stage of the disease (prevention versus treatment) and the anticipated side-effects in the intended patients (for example treatment of acne vulgaris in pubescent males).

Because of their valuable therapeutic potential, testosterone 5α-reductase inhibitors [hereinafter "5α-reductase inhibitors"] have been the subject of active research worldwide. For example, see: Hsia, S. and Voight, W., *J. Invest. Derm.*, **62**, 224 (1973); Robaire, B. *et al.*, *J. Steroid Biochem.*, **8**, 307 (1977); Petrow, V. *et al.*, *Steroids*, **38**, 121 (1981); Liang, T. *et al.*, *J. Steroid Biochem.*, **19**, 385 (1983); Holt, D. *et al.*, *J. Med. Chem.*, **33**, 937 (1990); U.S. Patent No. 4,377,584, U.S. Patent No. 4,760,071 and U.S. Patent No. 5,017,568. Two particularly promising 5α-reductase inhibitors are MK-906 (Merck), known by the generic name, finasteride, and marketed under the trademark, Proscar; and SKF-105657 (SmithKline Beecham), shown in Scheme B.

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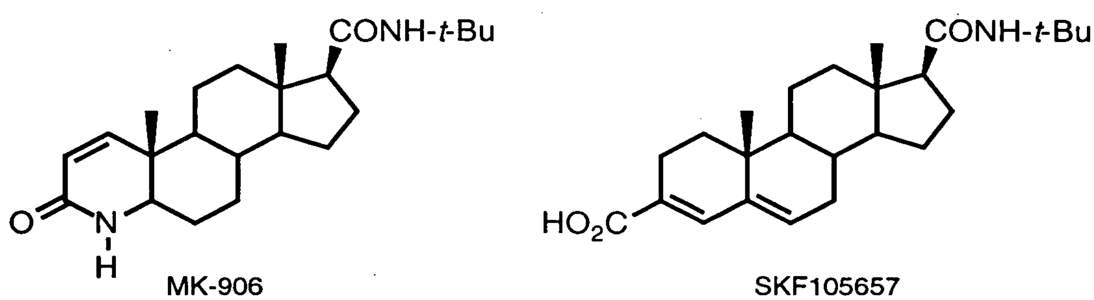

MK-906
finasteride

SKF105657

SCHEME B

The potent inhibition of bovine adrenal and porcine granulosa cell 3β-hydroxy-Δ^5-steroid dehydrogenase / 3-keto-Δ^5-steroid isomerase (3BHSD) by the

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4-azasteroid derivative, 4-MA, shown in Scheme C and not by the drug finasteride

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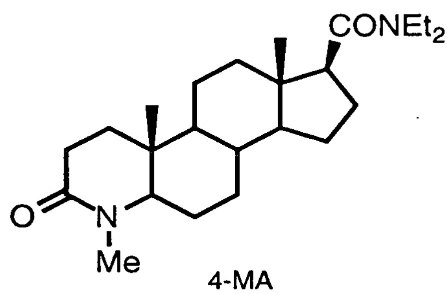

4-MA

SCHEME C

(Tan, C.H.; Fong, C.Y.; Chan, W.K. *Biochem. Biophys. Res. Comm.*, **144**, 166 (1987) and Brandt, M.; Levy, M.A. *Biochemistry*, **28**, 140 (1989)), along with the critical role of 3BHSD in steroid biosynthesis (Potts, G.O. *et al.*, *Steroids*, **32**, 257 (1978)), suggests that optimal inhibitors of type 1 and 2, 5α-reductase should also be selective versus human adrenal 3BHSD. The importance of selectivity in 5α-reductase inhibitors has been emphasized by reports of hepatotoxicity in certain 4-azasteroids such as 4-MA (McConnell, J.D. *The Prostate Suppl.*, **3**, 49 (1990) and Rasmusson, G.H. *et al. J. Med. Chem.* , **27**, 1690 (1984)).

SUMMARY OF THE INVENTION

One aspect of the present invention is the compound of formula (I),

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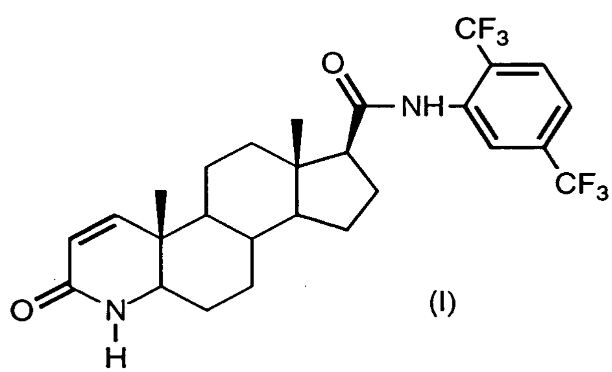

(I)

also known as 17β-N-(2,5-bis(Trifluoromethyl))phenylcarbamoyl-4-aza-5α-androst-1-en-3-one and pharmaceutically acceptable salts and solvates thereof.

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Other aspects of the invention are:

1. A method of inhibiting testosterone-5α-reductases comprising contacting testosterone-5α-reductases with the compound of formula (I).

2. A method of treatment of androgen responsive or mediated disease comprising administering an effective amount of the compound of formula (I) to a patient in need of such treatment.

3. Pharmaceutical formulations containing the compound of formula (I) as an active ingredient.

4. A method of treatment of androgen responsive or mediated disease comprising administering an effective amount of the compound of formula (I) to a patient in need of such treatment in combination with an anti-androgen such as flutamide.

5. A method of treatment of benign prostatic hyperplasia comprising administering an effective amount of the compound of formula (I) to a patient in need of such treatment in combination with an alpha 1 adrenergic receptor blocker (*e.g.* terazosin).

6. A method of treatment of benign prostatic hyperplasia comprising administering an effective amount of the compound of formula (I) to a patient in need of such treatment in combination with an anti-estrogen.

7. Intermediates produced in during the synthesis of the compound of formula (I).

DETAILED DESCRIPTION OF THE INVENTION

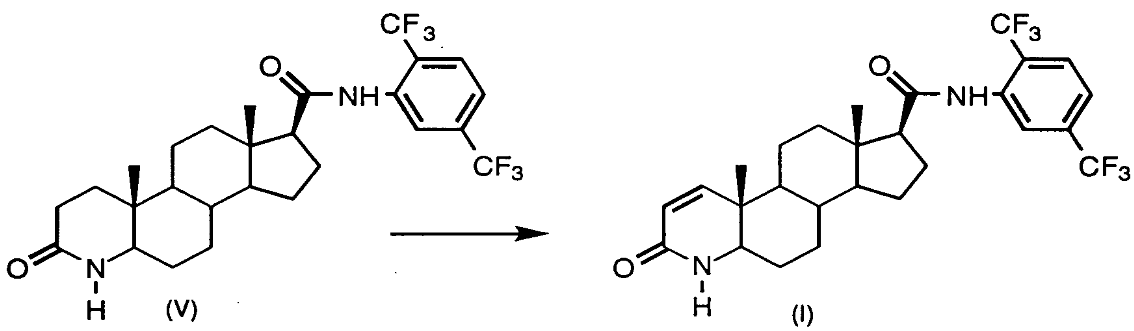
Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates". For example, a complex with water is known as a "hydrate". Solvates of compound (I) are within the scope of the invention.

It will also be appreciated by those skilled in organic chemistry that many

organic compounds can exist in more than one crystalline form. For example, crystalline form may vary from solvate to solvate. Thus, all crystalline forms of the compounds of formula (I) or the pharmaceutically acceptable solvates thereof are within the scope of the present invention.

Preparation of Compounds

The compound of the present invention may be prepared by the methods taught in US Patents 4,377,584 (hereinafter, "'584") and 4,760,071 (hereinafter, "'071") both incorporated herein by reference. For example, the compound of formula (I) may be prepared by the procedure shown in Scheme I and II.



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SCHEME I

In Scheme I, the compound of formula (V) is dehydrogenated to give the compound of formula (I) by treatment with a dehydrogenating system, *e.g.* 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and bis(trimethyl-silyl)trifluoroacet-amide in dry dioxane at room temperature for 2-5 hrs followed by heating at reflux for 10-20 hrs (see Bhattacharya, A. *et al.*, *J. Am. Chem. Soc.*, **110,** 3318 (1988)).

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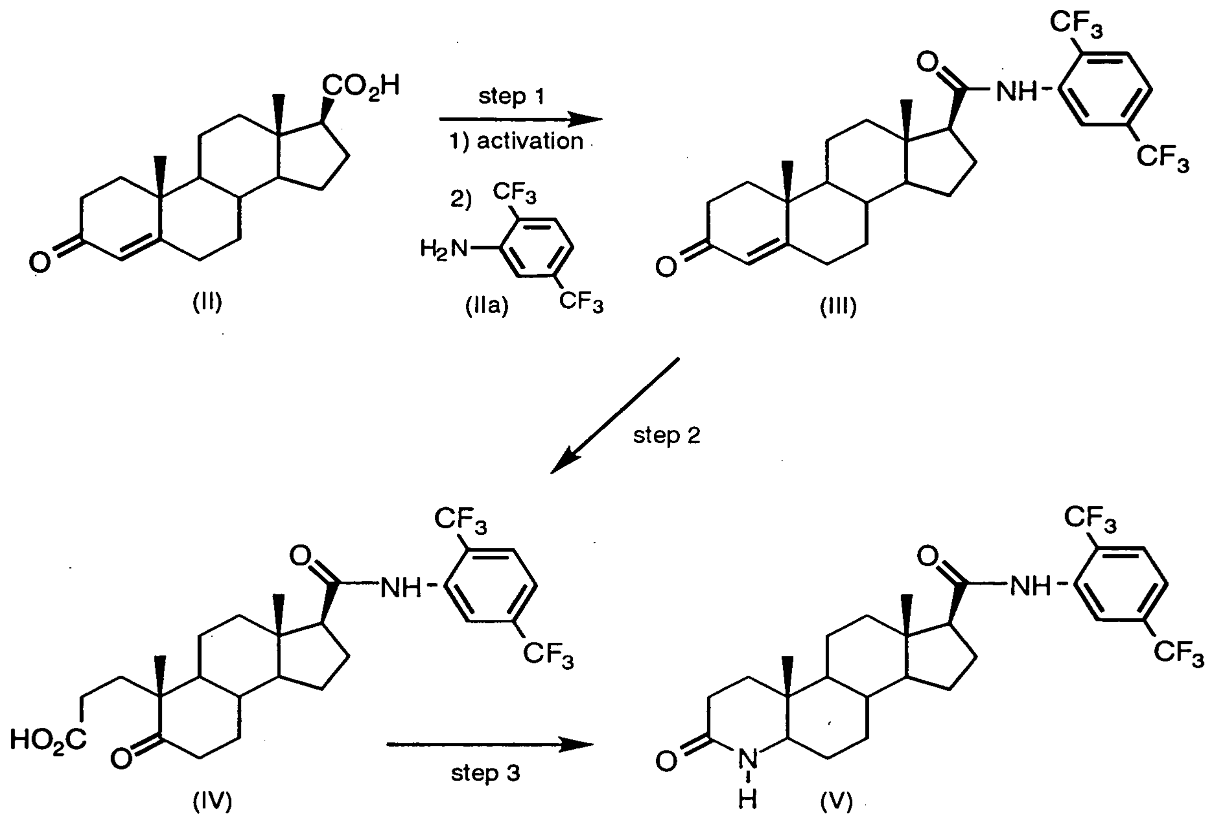
The compound of formula (V) may be prepared according to Scheme IA



SCHEME IA

In Step 1 of Scheme IA, 3-oxo-4-androstene-17β-carboxylic acid, (II) is converted to the corresponding amide of formula (III). This may be accomplished by activation of the acid and reaction with an aniline of formula (IIa). For example, the reaction sequence can be the conversion of a compound of formula (II) to the corresponding acid halide by treatment with a halogenating agent such as thionyl chloride or oxalyl chloride in an aprotic solvent such as toluene or methylene chloride at -5 to 10°C in the presence of a base such as pyridine.

The intermediate acid halide may be reacted with a substituted aniline of formula (IIa) at 25° to 100°C in an aprotic solvent such as toluene or methylene chloride to give the amide of formula (III). The compound of formula (IIa) is commercially available (Aldrich Chemical Company, Milwaukee, WI 53201).

In Step 2, the compound of formula (III) is converted to the 5-oxo-A-nor-3,5-secoandrostan-3-oic acid derivative of formula (IV) by oxidation, *e.g.* by

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treatment with aqueous sodium permanganate and sodium periodate under basic conditions at reflux in *t*-butanol.

In Step 3, the compound of formula (IV) is converted to the 4-aza-5α-androstan-3-one of formula (V) by treatment with ammonia at reflux in ethylene glycol followed by hydrogenation of the intermediate 4-aza-androst-5-en-3-one in acetic acid at 60 to 70°C and 40-60 psi hydrogen pressure in the presence of catalytic platinum oxide.

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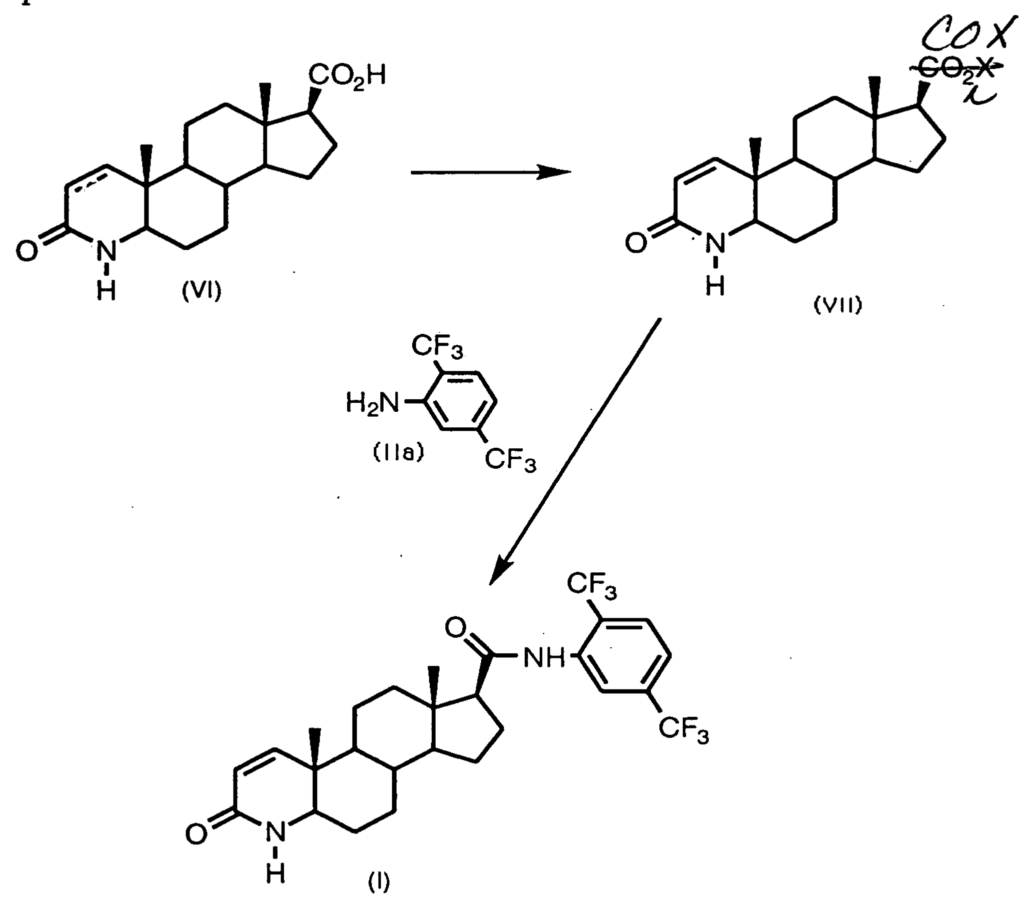

T80X

SCHEME II

Alternatively, in Scheme II, the compound of formula (I) may be prepared from the 3-oxo-4-aza-5α-androst-1-en-17β-carboxylic acid of formula (VI) (Rasmusson, G.H. *et al.*, *J. Med. Chem.*, **29**, 2298 (1986)), through the acid halide intermediate of formula (VII), wherein X is halogen, particularly chloro. The acid chloride of formula (VII) may be produced by treating the corresponding acid of formula (VI) with thionyl chloride in solvents such as toluene, heptane, acetonitrile, triethylphosphate, ethyl acetate, dimethylformamide, N-

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methylpyrrolidinone, dimethylimidazolidinone and dimethyltetrahydropyrimidinone. Persons skilled in the art will realize the addition of a catalytic amount of dimethylformamide can be utilized for acid chloride formation.

The intermediate of formula (VII) wherein X is halogen may be reacted with a substituted aniline of formula (IIa), commercially available (Aldrich Chemical Company, Milwaukee, WI 53201, at 25° to 100°C in an aprotic solvent such as toluene, heptane, acetonitrile, triethylphosphate, ethyl acetate, dimethylformamide, N-methylpyrrolidinone, dimethylimidazolidinone and dimethyltetrahydropyrimidinone to give the compound of formula (I). Bases such as dimethylaminopyridine to assist in the coupling can also be used. Alternative bases such as Diisopropylethylamine, triethylamine and 1,8-diazabicyclo[5.4.0]undec-7-ene might also be used in the preparation of the compound of formula (I). Persons skilled in the art will also realize that the addition of salts such as, LiCl and LiBr, might also be used to facilitate the coupling of the aniline of formula (IIa) with the acid halide of formula (VII) to produce the compound of formula (I).

Those skilled in the art will appreciate that at an earlier stage in the preparation of the compound of formula (I) or a solvate thereof it may have been necessary and/or desirable to protect one or more sensitive groups in the molecule to prevent undesirable side reactions.

The protecting groups used in the preparation of the compound of formula (I) may be used in a conventional manner. See for example Protective Groups in Organic Chemistry, Ed. J.F.W. McOmie, Plenum Press, London (1973) or Protective Groups in Organic Synthesis, Theodora Green, John Wiley and Sons, New York (1981).

Removal of any protecting groups present may be achieved by conventional procedures. An arylalkyl group such as benzyl, may be cleaved by hydrogenolysis in the presence of a catalyst, e.g., palladium on charcoal; an acyl group such as N-benzyloxycarbonyl may be removed by hydrolysis with, for example, hydrogen bromide in acetic acid or by reduction, for example by catalytic hydrogenation.

As will be appreciated, in any of the general processes described above it may be desirable or even necessary to protect any sensitive groups in the molecule as just described. Thus, a reaction step involving deprotection of a protected derivative of general formula (I) or a salt thereof may be carried out subsequent to any of the above described processes.

Thus, according to a further aspect of the invention, the following reactions may, if necessary and/or desired be carried out in any appropriate sequence subsequent to any of the general processes:

(i) removal of any protecting groups; and

(ii) conversion of a compound of formula (I) or a solvate thereof into a pharmaceutically acceptable solvate thereof.

As well as being employed as the last main step in the preparative sequence, the general methods indicated above for the preparation of the compounds of the invention may also be used for the introduction of the desired groups at an intermediate stage in the preparation of the required compound. It should therefore be appreciated that in such multi-stage processes, the sequence of reactions should be chosen in order that the reaction conditions do not affect groups present in the molecule which are desired in the final product.

The compound of formula (I) and the intermediate compounds, (II)-(VI), shown in Schemes I and II may be purified by convenient methods of the art, e.g., chromatography or crystallization.

In vitro Assays

Steroid 5α-Reductases

Enzyme activies may be determined using microsomes derived from: 1) prostate tissue from benign prostatic hyperplasia (BPH) patients; 2) recombinant baculovirus infected SF9 cells that express human type 1 5α-reductase; or 3) recombinant baculovirus infected SF9 cells that express human type 2 5α-reductase. Microsomes were prepared by homogenization of the tissue or cells, followed by differential centrifugation of the homogenate. Microsome extracts were incubated with varying concentrations of [1,2,6,7-3H]-testosterone, 1mM NADPH, and varying amounts of the compounds of Formula I, i.e. a test compound, in buffer containing a NADPH regenerating system capable of

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maintaining NADPH concentrations for a period of time within the range 0.5-240 minutes. Corresponding incubations were carried out with no test compound as a control study. For clone 1 IC_{50} measurements, assay components except testosterone were preincubated for 10 minutes at pH 7.0, and following the addition of 100nM testosterone the assays were allowed to proceed for 10-120 minutes. For clone 2 IC_{50} measurements, assay components except testosterone were preincubated for 20 minutes at pH 6.0, and following the addition of 8nM testosterone the assays were allowed to proceed for 20-40 minutes. The percentage of conversion of testosterone to DHT in the presence of test compounds compared to the corresponding conversion in the control study was estimated using high pressure liquid chromatography (HPLC) with radiochemical detection. The results of these assays appear as IC_{50}'s reported in Table 1.

<u>3β-Hydroxy-Δ^5-steroid Dehydrogenase / 3-Keto-Δ^5-steroid Isomerase</u>

Enzyme activities are measured using microsomes derived from human adrenal tissues. Microsomes were prepared by homogenization of the tissue followed by differential centrifugation of the homogenate. Microsome extracts were incubated with varying concentrations of dehydroepiandrosterone (DHEA), 1mM NAD+, and varying amounts of the compound of Formula (I), i.e. a test compound, in pH 7.5 buffer for a period of time within the range of 1 to 60 minutes. Corresponding incubations were carried out with no test compound as a control study. The percentage of conversion of DHEA to androstenedione in the presence of test compounds compared to the corresponding conversion in the control study was estimated using HPLC with radiochemical detection. The results of these assays appear as K_i's reported in Table 1.

TABLE 1

5α-Reductase (5αR) and Human Adrenal 3β-Hydroxy-Δ^5-Steroid Dehydrogenase /3-Keto-Δ^5-Steroid Isomerase (3βHSD) ***In Vitro*** **Inhibitory Activity**

T110X

IC_{50} Human Type 1 5AR	IC_{50} Human Type 2 5AR	K_i Human Adrenal 3BHSD
<1nM	<1nM	>1000nM

<u>*In vivo* Evaluation of Steroid 5α-Reductase Inhibitors</u>

The *in vivo* activity of steroid 5α-reductase inhibitors may be determined in a chronic rat model (Brooks, J.R. *et al.*, *Steroids*, **47**, 1 (1986)). The chronic

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model utilizes castrated male rats that are dosed daily with testosterone (20 μg/rat) subcutaneously and with test compound (0.01-10 mg/kg) or vehicle orally for 7 days. The animals are then sacrificed and their prostates weighed. Reduction in the size of testosterone-stimulated prostate weight demonstrated activity of the test compound. Known steroid 5α-reductase inhibitors were tested in parallel to ensure consistency of the assay method.

Utility

The steroid 5α-reductase inhibitor of the present invention is useful in the treatment of androgen responsive diseases , *e.g.*, benign and malignant diseases of the prostate, especially benign prostatic hyperplasia, in a manner similar to that for other 5α-reductase inhibitors such as finasteride and SKF105657. However, the compound of the present invention has a surprisingly long half-life and potency compared to finasteride and SKF105657. For correlation of *in vitro*, rat *in vivo* and human clinical data relating to an inhibitor of 5α-reductase, see Stoner, E. *et al.*, *J. Steroid Biochem. Molec. Biol.*, **37**, 375 (1990); Brooks, J.R. *et al.*, *Steroids*, **47**, 1 (1986) and Rasmusson, G.H. *et al.*, *J. Med. Chem.*, **29**, 2298 (1986)).

The compound of this invention is also useful in the treatment of prostatitis, prostate cancer, androgen mediated diseases of the skin, such as acne, hirsutism and male pattern baldness. Other hormone related diseases, *e.g.*, polycystic ovary disease, may also be treated with this compound.

The amount of the compound of formula (I) required to be effective as an 5α-reductase inhibitor will, of course, vary with the individual mammal being treated and is ultimately at the discretion of the medical or veterinary practitioner. The factors to be considered include the condition being treated, the route of administration, the nature of the formulation, the mammal's body weight, and surface area, age and general condition.of the mammal. However, for a human patient a suitable effective 5α-reductase inhibitory dose is in the range of about 0.001 to about 2 mg/kg body weight per day, preferably in the range of about 0.005 to about 1 mg/kg per day.

The total daily dose may be given as a single dose, multiple doses, *e.g.*, two to six times per day, or by intravenous infusion for a selected duration. Dosages above or below the range cited above are within the scope of the present

invention and may be administered to the individual patient if desired and necessary. For example, for a 75 kg mammal, a dose range would be about 0.04 mg to about 75 mg per day, and a typical dose would be about 10 mg per day. Because of the long half-life of the compound of the present invention, for many patients treatment may only be required every other day, even every third day and possibly less often. If discrete multiple doses are indicated, treatment might typically be 2.5 mg of a compound of formula (I) given 4 times per day.

Formulations

Formulations of the present invention for medical use comprise an active compound, i.e., the compound of formula (I), together with an acceptable carrier thereof and optionally other therapeutically active ingredients. The carrier must be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The present invention, therefore, further provides a pharmaceutical formulation comprising a compound of formula (I) together with a pharmaceutically acceptable carrier thereof.

The formulations include those suitable for oral, topical, rectal or parenteral (including subcutaneous, intramuscular and intravenous) administration. Preferred are those suitable for oral or parenteral administration.

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active compound into association with a carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active compound into association with a liquid carrier or a finely divided solid carrier and then, if necessary, shaping the product into desired unit dosage form.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets or lozenges, each containing a predetermined amount of the active compound; as a powder or granules; or a suspension or solution in an aqueous liquid or non-aqueous liquid, *e.g.*, a syrup, an elixir, an emulsion or a draught.

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A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active compound in a free-flowing form, *e.g.*, a powder or granules, optionally mixed with accessory ingredients, *e.g.*, binders, lubricants, inert diluents, surface active or dispersing agents. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered active compound with any suitable carrier.

A syrup or suspension may be made by adding the active compound to a concentrated, aqueous solution of a sugar, *e.g.*, sucrose, to which may also be added any accessory ingredients. Such accessory ingredient(s) may include flavoring, an agent to retard crystallization of the sugar or an agent to increase the solubility of any other ingredient, *e.g.*, as a polyhydric alcohol, for example, glycerol or sorbitol.

Formulations for rectal administration may be presented as a suppository with a conventional carrier, *e.g.*, cocoa butter or Witepsol S55 (trademark of Dynamite Nobel Chemical, Germany), for a suppository base.

Formulations suitable for parenteral administration conveniently comprise a sterile aqueous preparation of the active compound which is preferably isotonic with the blood of the recipient. Thus, such formulations may conveniently contain distilled water, 5% dextrose in distilled water or saline and the compound of the formula (I) that has an appropriate solubility in these solvents. Useful formulations also comprise concentrated solutions or solids containing the compound of formula (I) which upon dilution with an appropriate solvent give a solution suitable for parenteral administration above.

Topical formulations include ointments, creams, gels and lotions which may be prepared by conventional methods known in the art of pharmacy. In addition to the ointment, cream gel, or lotion base and the active ingredient, such topical formulation may also contain preservatives, perfumes, and additional active pharmaceutical agents.

In addition to the aforementioned ingredients, the formulations of this invention may further include one or more optional accessory ingredient(s) utilized in the art of pharmaceutical formulations, *e.g.*, diluents, buffers,

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flavoring agents, binders, surface active agents, thickeners, lubricants, suspending agents, preservatives (including antioxidants) and the like.

EXAMPLES

The following examples illustrate aspects of this invention but should not be construed as limitations. The symbols and conventions used in these examples are consistent with those used in the contemporary chemical literature, for example, the *Journal of the American Chemical Society*. As used here in the term "room temperature" means about 25°C.

Example 1
17β-N-(2,5-bis(Trifluoromethyl))phenylcarbamoyl-4-aza-5α-androst-1-en-3-one
(Synthesis of Scheme I)

A. 17β-N-(2,5-bis(Trifluoromethyl))phenylcarbamoyl-androst-4-en-3-one

To a solution of 3-oxo-4-androstene-17β-carboxylic acid (Rasmusson, G.H. *et al., J. Med. Chem.*, **27**, 1690 (1984)) (17.2 g, 54.4 mmol), dry THF (180 mL) and dry pyridine (7 ml) at 2°C is added thionyl chloride (5.1 mL, 70.8 mmol). The reaction mixture is stirred at 2°C for 20 min and then stirred at room temperature for 40 min. The reaction mixture is then filtered and the solid washed with toluene. The filtrate is concentrated *in vacuo* to an oil which is diluted with dry THF (150 mL) and dry pyridine (7 mL). To the resultant dark solution is added 2,5-bis-(trifluoromethyl)aniline (9.4 mL, 59.8 mmol) and the reaction mixture is refluxed for 5 h, diluted with methylene chloride, extracted sequentially with 1N HCl and brine, dried over sodium sulfate, and filtered. The filtrate is concentrated and applied to a column of 500 g of silica gel and the column eluted with a 15-30% ethyl acetate - hexane gradient to give, after concentration, 17β-N-(2,5-bis(trifluoromethyl))phenyl-carbamoyl-androst-4-en-3-one as an off-white foam.

B. 17β-N-(2,5-bis(Trifluoromethyl))phenylcarbamoyl-5-oxo-A-nor-3,5-secoandrostan-3-oic acid

To a refluxing solution of 17βN-(2,5-bis(trifluoromethyl))phenylcarbamoyl-androst-4-en-3-one (18.3 g, 34.9 mmol) prepared as in part A above, *t*-butanol (275 mL), sodium carbonate (6.3 g, 50.8 mmol), and water (36 mL) is added, over 45 min, a 75°C solution of potassium

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permanganate (0.38g, 2.4 mmol), sodium periodate (52.2g , 245 mmol) and water (311 mL). After refuxing an additional 15 min, the heterogeneous mixture is cooled to room temperature and celite (50 g) is added. The reaction mixture is filtered through a bed of celite (50 g) and the solid is washed with water and the filtrate concentrated *in vacuo* to remove *t*-butanol (ca. 175 ml). The resultant aqueous solution is acidified to pH 2 with 36% HCl and the extracted 4 times with chloroform. The chloroform layers are combined and washed with water, brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to give 17β-N-(2,5-bis(trifluoromethyl))phenylcarbamoyl-5-oxo-A-nor-3,5-secoandros-tan-3-oic acid as a off-white solid. This material is carried directly into step C below.

C. 17β-N-(2,5-bis(Trifluoromethyl))phenylcarbamoyl-4-aza-androst-5-en-3-one

To a suspension of 17β-N-(2,5-bis(trifluoromethyl))phenylcarbamoyl-5-oxo-A-nor-3,5-secoandrostan-3-oic acid (20.5 g, 34.8 mmol), as prepared in step B, in dry ethylene glycol (100 mL) at room temperature is added ammonia (ca. 8 mL, 0.32 mol) over a 5 min period. The resultant solution is heated to 180°C over 45 min, and after 12 min at 180°C, the reaction mixture is cooled to 70°C and water (116 mL) is added over a period of 5 min. The resultant suspension is cooled to 7°C and stirred for 10 min and filtered under vacuum. The solid is washed with water (60 mL) and then is dissolved in chloroform and washed with water, brine, dried over sodium sulfate, filtered and concentrated. The residue is dissolved in chloroform and applied to a column of 110 g of silica gel and the column eluted with a 2-5% isopropanol-chloroform gradient to give 17β-N-(2,5-bis(trifluoromethyl))phenyl-carbamoyl-4-aza-androst-5-en-3-one as an off-white solid.

D. 17β-N-(2,5-bis(Trifluoromethyl))phenylcarbamoyl-4-aza-5α-androstan-3-one

To a solution of 17β-N-(2,5-bis(trifluoromethyl))phenylcarbamoyl-4-aza-androst-5-en-3-one (8.9g, 16.7 mmol) in acetic acid (120 mL) is added platinum oxide (0.9 g). The resultant mixture is charged to 50 psi with hydrogen and heated at 60-70°C for 6 h. After replacing the hydrogen atmosphere with nitrogen, the reaction mixture is filtered through celite and the celite pad washed with acetic acid (30 mL), chloroform (60 mL) and toluene (200 mL). The filtrate is concentrated *in vacuo* to an oil, toluene (200 mL) is added and the solution concentrated to a foam *in vacuo*. The foam is crystallized from ethyl acetate-heptane to give, after drying *in vacuo* at 85°C for 1 h, 17β-N-(2,5-bis(trifluoromethyl))phenylcarbamoyl-4-aza-5α-androstan-3-one; m.p. 245-247°C.

Anal. Calcd. for $C_{27}H_{32}F_6N_2O_2$: C, 61.12 ; H, 6.08 ; N, 5.28. Found: C, 61.13; H, 6.12; N, 5.21.

E. 17β-N-(2,5-bis(Trifluoromethyl))phenylcarbamoyl-4-aza-5α-androstan-1-en-3-one

To a suspension of 17β-N-(2,5-bis(Trifluoromethyl))phenylcarbamoyl-4-aza-5α-androstan-3-one (7.24 g, 13.7 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (3.41 g, 15 mmol) in dry dioxane (168 mL) at room temperature is added bis(trimethylsilyl)trifluoroacetamide (14.5 mL, 54.6 mmol). After stirring at room temperature for 7 h, the reaction mixture is refluxed for 18 h. The resultant dark solution is cooled to room temperature and is concentrated *in vacuo* to a dark oil. Methylene chloride (100 mL) and a 1% sodium bisulfite solution (40 mL) is added to the oil and the two phase mixture is stirred rapidly for 15 min and filtered. The two filtrate layers are separated and the methylene chloride layer is washed sequentially with 2N HCl and brine, dried over sodium sulfate, filtered, and concentrated to a brown oil. The oil is diluted with toluene and is applied to a column of 300 g of silica gel and eluted with a 12:3:1 to 9:3:1 gradient of toluene:acetone:ethyl acetate to give 17β-N-(2,5-bis(trifluoromethyl))phenyl-carbamoyl-4-aza-5α-androst-1-en-3-one as a foam. This material is crystallized from ethyl acetate-heptane (1:1) to give a white solid; m.p. 244-245°C.
^{13}C NMR (100 MHz, $CHCl_3$) d 171.31, 166.77, 151.04, 136.35 (q, J = 1.4 Hz), 135.01 (q, J = 33.1 Hz), 126.73 (q, J = 5.4 Hz), 123.44 (q, J = 273.5 Hz), 123.03 (q, J = 273.2 Hz), 122.84, 121.58 (qq, J = 30.4, 1.0 Hz), 120.37 (q, J = 3.6 Hz), 120.29 (q, J = 3.9 Hz), 59.58, 58.33, 55.69, 47.46, 44.78, 39.30, 37.81, 35.29, 29.34, 25.70, 24.17, 23.59, 21.15, 13.40, 11.91.
Anal. Calcd. for $C_{27}H_{30}F_6N_2O_2$: C, 61.36 ; H, 5.72 ; N, 5.30. Found: C, 61.36; H, 5.73; N, 5.23.

Example 2
17β-N-(2,5-bis(Trifluoromethyl))phenylcarbamoyl-4-aza-5α-androst-1-en-3-one
(Synthesis of Scheme II)

A solution of 3-oxo-4-aza-5a-androst-1-en-17β-carboxylic acid (31.7 g, 100 mmol) in pyridine (800 mL) is cooled to -10°C, and thionyl chloride (14.3 g, 120 mol) is added with stirring. The mixture is allowed to stir 2.5 - 3 hours at 20°C, to form the acid chloride (17β-chlorocarbonyl-4-aza-5α-androst-1-en-3-one); IR 1780 cm^{-1}, FAB-MS $[MH]^+$ = 336.

To the stirring acid chloride 2,5-bis(trifluoromethyl)aniline (23.1 g, 101

17

mol) is added. Stirring is continued for 4-6 hours, 960 mL of water is added and the slurry is stirred at room temperature overnight. Filtration gives the crude product as an off-white solid. The crude solid is recrystallized by dissolution in 725 mL of acetonitrile at 70°C and removal of acetonitrile by distillation gives, after cooling and filtration, 17β-N-2,5-bis(Trifluoromethyl)phenylcarbamoyl-4-aza-5α-androst-1-en-3-one as a white crystalline solid.

Example 3

Pharmaceutical formulations

"Active compound" is the compound of Formula (I).

(A) Transdermal System - For 1000 Patches

T180X

Ingredients	Amount
Active compound	40 g
Silicone fluid	450 g
Colloidal silicon dioxide	25 g

The silicone fluid and active compound are mixed together and the colloidal silicone dioxide is added to increase viscosity. The material is then dosed into a subsequently heat sealed polymeric laminate comprised of the following: polyester release liner, skin contact adhesive composed of silicone or acrylic polymers, a control membrane which is a polyolefin (*e.g.* polyethylene, polyvinyl acetate or polyurethane), and an impermeable backing membrane made of a polyester multilaminate. The resulting laminated sheet is then cut into 10 sq. cm patches.

(B) Oral Tablet - For 1000 Tablets

T181X

Ingredients	Amount
Active compound	20 g
Starch	20 g
Magnesium Stearate	1 g

The active compound and the starch are granulated with water and dried. Magnesium stearate is added to the dried granules and the mixture is thoroughly blended. The blended mixture is compressed into tablets.

(C) Suppository - For 1000 Suppositories

TR10C

Ingredients	Amount
Active compound	25 g
Theobromine sodium salicylate	250 g
Witepsol S55	1725 g

The inactive ingredients are mixed and melted. The active compound is then distributed in the molten mixture, poured into molds and allowed to cool.

(D) Injection - For 1000 Ampules

TR11X

Ingredients	Amount
Active Compound	5 g
Buffering Agents	q.s.
Propylene glycol	400 mg
Water for injection	600 mL

The active compound and buffering agents are dissolved in the propylene glycol at about 50°C. The water for injection is then added with stirring and the resulting solution is filtered, filled into ampules, sealed and sterilized by autoclaving.

(E) Capsule - For 1000 Capsules

T192X

Ingredients	Amount
Active Compound	20 g
Lactose	450 g
Magnesium stearate	5 g

The finely ground active compound is mixed with the lactose and stearate and packed into gelatin capsules.